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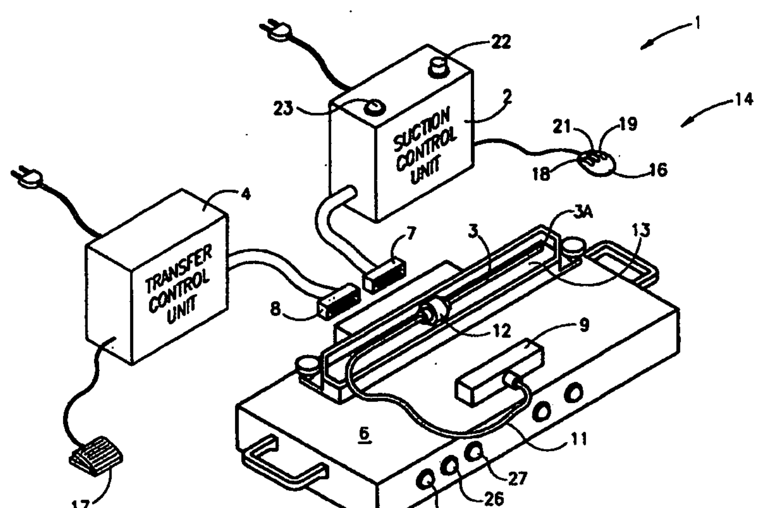
(54) Title: METHOD FOR DEPOSITING A FLATTENED DROPLET ON A SURFACE AND APPARATUS THEREFOR, AND A PUMP THEREFOR

(57) Abstract

A method and apparatus therefor for depositing a flattened droplet on a partially absorbent surface comprising the steps of providing a narrow bore transfer tube having a proximal end and a distal end and containing a microvolume of liquid, the proximal end connected to a pneumatic system adapted for issuing an outgoing flow of displacement gas into the tube and drawing an incoming flow of displacement gas therefrom; and issuing an outgoing flow of displacement gas for slowly discharging substantially the entire microvolume of liquid as a droplet on the surface and controllably blowing one or more bubbles into the droplet towards the end of its discharge for flattening the droplet on the surface. A pump (31) comprising a housing (33) having a bore (34) with an internal peripheral surface (36), and a stationary annular sealing member (48) integrally formed therewith at a first end (37) of a pair of opposite ends (37 and 38); a slide rod (39) disposed in the bore and having an external peripheral surface (41) and a displaceable annular sealing member (49) integrally formed therewith; the sealing members sealing the peripheral surfaces to define a vented displacement volume (51) therebetween whose volume is proportional to an annular cross section area between the peripheral surfaces and a distance between the sealing members; and the slide rod being slidably reciprocable between first and second positions respectively toward and away from the stationary sealing member whereupon the displaceable sealing member moves to reduce the volume to issue an outgoing flow of displacement gas from the displacement volume on a downstroke of the slide rod from its second position to its first position and the displaceable sealing member moves to increase the volume to draw an incoming flow of displacement gas into the displacement volume on an uspstroke of the slide rod from its first position to its second position.



METHOD FOR DEPOSITING A FLATTENED DROPLET ON A SURFACE AND APPARATUS THEREFOR, AND A PUMP THEREFOR

FIELD OF THE INVENTION

The invention relates to a method for depositing a flattened droplet on a surface suitable for *in vitro* fertilization (IVF) and embryo transfer (ET), and apparatus therefor, and a pump therefor.

BACKGROUND OF THE INVENTION

In an IVF-ET procedure, oocytes are aspirated from female ovaries and inseminated *in vitro* with male sperm in a culture medium to form embryos which are incubated prior to their being transferred to a subject by means of a two-stage transfer procedure. The transfer procedure includes the aspiration of a relatively large volume of about 20-40 μl of culture medium containing between one to five embryos into a transfer catheter by means of a manually operated syringe and its subsequent injection into a subject.

Since a conventional IVF-ET procedure is manual, the rate of injection of the embryo containing culture into a uterine cavity may vary significantly. Thus, on the one hand, too slow an injection rate may cause embryo containing culture medium to trickle down the transfer catheter's outer surface and, on the other hand, too quick an injection rate may severely damage embryo(s) following their collision against a uterine wall. The latter case may also flood a subject's uterus possibly resulting in a failed procedure as embryos are either washed out of her uterus or implanted in one of her Fallopian tubes leading to an ectopic pregnancy. Another disadvantage attendant with the use of a relatively large volume of culture medium is that it may alter the specific properties of the micro-environment within a subject's uterus required for successful embryo implantation and its normal development.

The present invention is based on the notion that substantially automating embryo implantation in IVF-ET procedures may overcome some of the shortcomings of the conventional IVF-ET procedure.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a method for depositing a flattened droplet on a surface particularly suitable for depositing embryo(s) containing culture medium at a desired site in a uterus cavity, and apparatus therefor, and a pump therefor.

In accordance with a first aspect of the invention, there is provided a method for depositing a flattened droplet on a partially absorbent surface, the method comprising the steps of:

(a) providing a narrow bore transfer tube having a proximal end and a distal end and containing a microvolume of liquid, the proximal end connected to a pneumatic system for issuing an outgoing flow of displacement gas into the transfer tube and drawing an incoming flow of displacement gas thereinto from the transfer tube; and

(b) issuing an outgoing flow of displacement gas for slowly discharging substantially the entire microvolume of liquid as a droplet on the surface-and controllably blowing one or more bubbles into the droplet towards the end of its discharge to flatten the droplet on the surface.

A *"flattened droplet"* in the context of the present invention can be demonstrated on standard 80 gram/m^2 A4 paper for use with ink jet printers, such paper constituting a partially absorbent surface on which a flattened droplet of the present invention has a projected surface area about three to six times larger than that of a naturally forming dome-like droplet. A *"partially absorbent surface"* in the context of the present invention is one which absorbs a relatively insignificant volume of a naturally forming dome-like droplet over about 60 seconds. The flattening of a droplet as achieved by the method of the present invention is not by the relatively slow process of its being absorbed assuming it does not dry but rather as a consequence of its being effectively inflated by one or more bubbles of displacement gas controllably blown thereinto towards the end of its discharge which typically occurs over 5-20 seconds from an initial outward displacement of the microvolume of liquid. The surface may be flat, inclined or even inverted and still maintain the droplet in its flattened shape by virtue of the prevailing surface tension therewith.

A *"microvolume of liquid"* in the context of the present invention is a volume of liquid in the microliter range, e.g., within the range of 0.05-5 μl, preferably within the range of 0.1-3.0 μl, and particularly within the range of 0.3-2.0 μl. In the case of an IVF-ET procedure on a human subject when the catheter is upwardly inclined, even though the discharge of culture medium is relatively slow, its volume is so small so as to avoid a downward trickle along the catheter's outer surface.

In accordance with a preferred embodiment of the present invention, step (a) includes:

(a1) preventing capillary forces to draw liquid into the transfer tube upon insertion of its distal end into a vessel containing liquid;

(a2) inserting the transfer tube's distal end into the liquid;

(a3) drawing an incoming flow of displacement gas from the transfer tube such that a microvolume of liquid is drawn thereinto; and

(a4) removing the transfer tube's distal end from the liquid.

The step of preventing capillary forces is preferably achieved by issuing an outgoing flow of displacement gas into the transfer tube so as to create a positive pressure therein. Alternatively, this step can be achieved, for example, by providing a seal at its distal end. After the transfer tube's distal end is removed from the liquid, the microvolume of liquid is preferably inwardly drawn away from its distal end as a safety precaution whereafter the inward displacement is neutralized by a brief outgoing flow of displacement gas into the transfer tube.

After the discharge of the microvolume of liquid from the transfer tube, the flattened droplet in most cases is still connected to the transfer tube's distal end and therefore to prevent its suction back into the transfer tube, the outgoing flow of displacement gas is maintained until the droplet is disconnected from the transfer tube's distal end by manually withdrawing the transfer tube. This outgoing flow of displacement gas may also remove any small quantities of the microvolume which were not initially discharged and which may include an embryo(s) in an IVF-ET procedure.

In accordance with a second aspect of the present invention, there is provided apparatus for depositing a flattened droplet of liquid on a partially absorbent surface, the apparatus for use with a narrow bore transfer tube having a proximal end

and a distal end and a vessel of liquid, the apparatus comprising:

(a) a pneumatic system connected to the transfer tube's proximal end and adapted for issuing an outgoing flow of displacement gas into said transfer tube and drawing an incoming flow of displacement gas thereinto from said transfer tube; and

(b) a control mechanism for controlling said pneumatic system in different operational modes including:

- a user controlled suction mode for drawing an incoming flow of displacement gas from the transfer tube whereby a microvolume of liquid is drawn thereinto prior to the removal of said distal end from the vessel; and
- a user initiated automated delivery mode for issuing an outgoing flow of displacement gas into the transfer tube for slowly discharging substantially the entire microvolume of liquid as a droplet on the surface and controllably blowing one or more bubbles into the droplet towards the end of its discharge to flatten the droplet on the surface.

In accordance with a third aspect of the present invention, there is provided a pump comprising a housing having a bore with an internal peripheral surface, and a stationary annular sealing member integrally formed therewith at a first end of a pair of opposite ends; a slide rod disposed in said bore and having an external peripheral surface and a displaceable annular sealing member integrally formed therewith; said sealing members sealing said peripheral surfaces to define a vented displacement volume therebetween whose volume is proportional to an annular cross section area between said peripheral surfaces and a distance between said sealing members; and said slide rod being slidably reciprocable between first and second positions respectively toward and away from said stationary sealing member whereupon said displaceable sealing member moves to reduce said volume to issue an outgoing flow of displacement gas from said displacement volume on a downstroke of said slide rod from said second position to said first position and said displaceable sealing member moves to increase said volume to draw an incoming flow of displacement gas into said displacement volume on an upstroke of said slide rod from said first position to said second position.

Preferably both the bore and the slide rod are of a right cylindrical shape such that the displacement volume has a cross sectional area defined by $\pi(a^2-b^2)$ where a and b are the radii of the bore's internal peripheral surface and the slide rod's external peripheral surface, respectively. Preferably, the cross section area is in the order of 4-10 mm^2 and the pump has a displacement volume incrementally changeable in the order of 0.1-0.4μl.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and how it is used, a preferred embodiment will now be described by way of a non-limiting example only, with reference to the accompanying drawings in which:

Fig. 1 is a pictorial view of apparatus for depositing a flattened droplet on a surface in accordance with the present invention;

Figs. 2A-2L illustrates operation of the apparatus of Figure 1 for depositing the flattened droplet on the surface;

Fig. 3 is a pictorial view of a pump in accordance with the present invention; and

Figs. 4 and **5** are cross sectional views of the pump of Figure 3 along lines A-A and B-B in Figure 3, respectively.

DETAILED DESCRIPTION OF THE DRAWINGS

With reference now to Figures 1 and 2, apparatus **1** is employed for depositing a flattened droplet **F** on a partially absorbent surface **S**, for example, on a subject's endometrium in an IVF-ET procedure. Apparatus **1** includes a suction control unit **2** normally permanent located in a laboratory for the preparation of an embryo carrying catheter **3** constituting a transfer tube, a transfer control unit **4** normally permanently located in a treatment room where an IVF-ET procedure is carried out and a portable casing **6** for consecutive connection to the suction control unit **2** and the transfer control unit **4** by means of connectors **7** and **8**. The casing **6** includes a pneumatic system **9** which is permanently connected to the catheter **3** during an entire IVF-ET procedure via suitable air tubing **11** and an air filter **12**. The casing **6** also has a

receptacle **13** for accommodating the catheter **3** during its transport from the laboratory to the treatment room.

The pneumatic system **9** is under a control mechanism **14** including a computer mouse **16** for controlling the suction control unit **2** for initiating a user controlled suction mode to prepare the catheter **3** with a microvolume of embryo containing culture medium and a foot pedal **17** for controlling the transfer control unit **4** for initiating a user initiated automated delivery mode for depositing the flattened droplet **F** on the surface **S**. The computer mouse **16** has an upstroke control **18** for drawing an incoming flow of displacement gas into the pneumatic system **9** from the catheter **3**, a downstroke control **19** for issuing an outgoing flow of displacement gas from the pneumatic system **9** into the catheter **3** and optionally a speed control **21** for controlling the flow rate of the displacement gas either from or into the pneumatic system **9**. The suction control unit **2** is also provided with a reset button **22** for priming the pneumatic system **9** for a pre-suction mode of issuing an outgoing flow of displacement gas as indicated by a READY indicator light **23** prior to the preparation of the catheter **3**. The different stages of the automatic delivery mode are indicated by a READY indicator light **24**, a GO indicator light **26** and a DONE indicator light **27**.

In operation, the casing **6** is initially connected to the suction control unit **2** and the catheter **3** is connected to the pneumatic system **9** via the air tubing **11** and the filter **12**. An operator presses the reset button **22** whereupon a lit READY indicator light **23** indicates an outgoing flow of displacement gas creating a positive pressure within catheter **3** to prevent capillary forces drawing culture medium thereinto upon insertion of its distal end **3A** into a vessel of culture medium **C** containing embryos **E** shown exaggerated in all Figs. 2A-2L (see Fig. 2A). The operator inserts the distal end **3A** into the vessel of culture medium **C** for aspirating about 0.3 to 0.6 μl microvolume of culture medium containing an embryo **E** into the catheter **3** (see Fig. 2B). Once an embryo is clearly seen to be close to the catheter's distal end **3A**, the rate of aspiration of culture medium may be increased by depressing the speed control **21**. If a single embryo is to be transferred, distal end **3A** is then be removed from the culture medium otherwise additional embryos may be captured as shown.

Once the catheter **3** contains one or more embryos, the operator withdraws

its distal end **3A** from the culture medium and then proceeds to depress the downstroke control **19** to slowly displace the microvolume of culture medium inwardly (see Fig. 2C). After the microvolume of culture medium has been inwardly displaced by about 5-15 mm from the catheter's distal end **3A**, its motion is arrested by a momentary outgoing flow of displacement gas (see Fig. 2D) so that it finally comes to rest at a distance of about 10 mm (see Fig. 2E) therefrom thereby ensuring that it cannot be inadvertently lost during transportation of the casing **6** between the laboratory and the treatment room. The catheter **3** is then placed in the receptacle **13** (see Fig. 1) during the transportation of the casing **6** from the laboratory to the treatment room.

For transfer of the embryos **E** onto the surface **S**, the catheter **3** is laid on the surface **S** (see Fig. 2F) whereupon a first depression on the foot pedal **17** causes the READY indicator light **24** to be lit indicating that the automatic delivery mode can be initiated. Thereafter, a second depression on the foot pedal **17** causes the GO indicator light **26** to be lit indicating that an outgoing flow of displacement gas is displacing the microvolume of culture medium towards the catheter's distal end **3A** (see Fig. 2G). The outgoing flow of displacement gas causes a concave shaped meniscus to be slowly formed which increases in size until it suddenly ruptures whereby most of the microvolume of culture medium is discharged as a droplet **D** on the surface **S** (see Figs. 2H and 2J). The discharge is accompanied by one or more air bubbles **B** for effectively inflating the droplet **D** thereby considerably widening its projected surface area on the surface **S** to form the flattened droplet **F** whose shape is maintained by its prevailing surface tension with the surface **S** (see Fig. 2K).

The GO indicator light **26** is then extinguished indicating that the operator should slightly withdraw the catheter **3** so as to detach it from the droplet **F** whilst at the same time there is an outgoing flow of displacement gas (see Fig. 2L). In the case of an actual IVF-ET procedure, withdrawal is limited to between about 10-15 mm such that the catheter's distal end **3A** still lies along a subject's endometrium. Finally, a further outgoing flow of additional displacement gas is provided so as to remove any culture medium which may remain in the catheter **3**. The DONE indicator light **27** is then lit to indicate that the catheter **3** can be completely removed.

With reference now to Figures 3-5, a pump **31** constituting a pneumatic

system for use with the apparatus **1** includes a base **32** with a housing **33** having a longitudinal right cylindrical throughbore **34** with an internal peripheral surface **36** of a radius a and having first and second opposite ends **37** and **38**. A right cylindrical slide rod **39** with an external peripheral surface **41** of a radius b and first and second opposite end **42** and **43** is disposed in the bore **34** and is slidingly reciprocated by means of a linear actuator screw **44** driven by a step motor **46**.

A sleeve bearing **47** having a sealing O-ring gasket **48** constituting a stationary annular sealing member is disposed at the first end **37** and an O-ring gasket **49** constituting a displaceable annular sealing member is disposed at the slide rod end **42**, the gaskets **48** and **49** sealingly the peripheral surfaces **36** and **41** to define a displacement volume **51** vented by a vent **52**. The displacement volume **51** has a volume equal to a product of a cross sectional area between the surfaces **36** and **41** defined by $\pi(a^2-b^2)$ and the distance between the gaskets **48** and **49**.

The slide rod **39** is slidingly reciprocable between first and second positions respectively toward and away from the gasket **48** whereupon the displacement volume **51** has a minimum value when the gaskets **48** and **49** are adjacent in which case a major portion of the slide rod **39** is exterior to the bore **34** and a maximum value when the gaskets **48** and **49** are remote from one another. In operation, the gasket **49** moves to reduce the volume of the displacement volume **51** to issue an outgoing flow of displacement gas therefrom on a downstroke of the slide rod **39** from its second position to its first position and the gasket **49** moves to increase the volume of the displacement volume **51** to draw an incoming flow of displacement gas thereinto on an upstroke of the slide rod **39** from its first position to its second position.

The bore **34** and the slide rod **39** typically have diameters in the range of about 5-10 mm and which differ in the range of about 0.3-0.7 mm such that the cross section area is in the order of about 4-10 mm^2. The threading on actuator screw **44** is designed such that each step of the motor **45** causes an incremental movement of the slide rod **39** of about 0.001-0.002 inches. The motor **45** is typically driven at a rate of about 20-300 steps per second.

Various modifications and changes may be made in the configuration described above that come within the spirit of the invention. The invention embraces all such changes and modifications coming within the scope of the appended claims.

CLAIMS:

1. A method for depositing a flattened droplet on a partially absorbent surface comprising the steps of:

(a) providing a narrow bore transfer tube having a proximal end and a distal end and containing a microvolume of liquid, the proximal end connected to a pneumatic system adapted for issuing an outgoing flow of displacement gas into the tube and drawing an incoming flow of displacement gas therefrom; and

(b) issuing an outgoing flow of displacement gas for slowly discharging substantially the entire microvolume of liquid as a droplet on the surface and controllably blowing one or more bubbles into the droplet towards the end of its discharge for flattening the droplet on the surface .

2. The method of claim 1 wherein step (a) includes:

(a1) preventing capillary forces to draw liquid into the transfer tube upon the insertion of its distal end into a vessel containing liquid;

(a2) inserting the transfer tube's distal end into the vessel;

(a3) drawing an incoming flow of displacement gas from the transfer tube such that a microvolume of liquid is drawn thereinto; and

(a4) removing the transfer tube's distal end from the liquid.

3. The method of claim 2 wherein step (a1) includes issuing an outgoing flow of displacement gas into the transfer tube.

4. The method of claim 3 further comprising the step of:

(a5) drawing the microvolume of liquid into the transfer tube away from its distal end; and

(a6) neutralizing the inward displacement by a brief outgoing flow of displacement gas into the transfer tube.

5. The method according to any one of claims 1-4 further comprising the step of:

(c) providing an additional outflow of displacement gas while displacing the transfer tube away from the droplet so separate the droplet from its distal end.

6. The method according to any one of claims 1-5 wherein the microvolume of liquid is a culture medium containing embryo(s) which are urged against the surface by the droplet's prevailing surface tension.

7. Apparatus for depositing a flattened droplet on a partially absorbent surface, the apparatus for use with a narrow bore transfer tube having a proximal end and a distal end and a vessel of liquid, the apparatus comprising:

(a) a pneumatic system connected to the transfer tube's proximal end and adapted for issuing an outgoing flow of displacement gas into said transfer tube and drawing an incoming flow of displacement gas thereinto from said transfer tube; and

(b) a control mechanism for controlling said pneumatic system in different operational modes including:

- an user controlled suction mode for drawing an incoming flow of displacement gas from said transfer tube whereby a microvolume of liquid is drawn thereinto prior to the removal of said distal end from the vessel; and
- an user initiated automated delivery mode for issuing an outgoing flow of displacement gas into said transfer tube for slowly discharging substantially the entire microvolume of liquid as a droplet on the surface and controllably blowing one or more bubbles into the droplet towards the end of its discharge for flattening the droplet on the surface.

8. Apparatus according to Claim 7 wherein said control mechanism includes an automatic pre-suction mode for issuing an outgoing flow of displacement gas.

9. Apparatus according to Claim 7 or 8 wherein separate units house a suction control unit for controlling said user controlled suction mode and a transfer control unit for controlling said user initiated automatic delivery mode.

10. A pump comprising a housing having a bore with an internal peripheral surface, and a stationary annular sealing member integrally formed therewith at a first end of a pair of opposite ends; a slide rod disposed in said bore and having an external peripheral surface and a displaceable annular sealing member integrally formed therewith; said sealing members sealing said peripheral surfaces to define a vented displacement volume therebetween whose volume is proportional to an annular cross section area between said peripheral surfaces and a distance between said sealing members; and said slide rod being slidably reciprocable between first and second positions respectively toward and away from said stationary sealing member whereupon said displaceable sealing member moves to reduce said volume to issue an outgoing flow of displacement gas from said displacement volume on a downstroke of said slide rod from said second position to said first position and said displaceable sealing member moves to increase said volume to draw an incoming flow of displacement gas into said displacement volume on an upstroke of said slide rod from said first position to said second position.

11. The pump according to claim 10 wherein both said bore and said slide rod are of right cylindrical shape and said cross section area is defined by $\pi(a^2-b^2)$ where a and b are the radii of said internal peripheral surface and said external peripheral surface, respectively.

12. The pump according to either claim 10 or 11 wherein said cross section area has an area of about 4-10 mm^2.

13. The pump according to any one of claims 10-12 wherein said displacement volume can be incrementally changed in the order of 0.1-0.4μl.

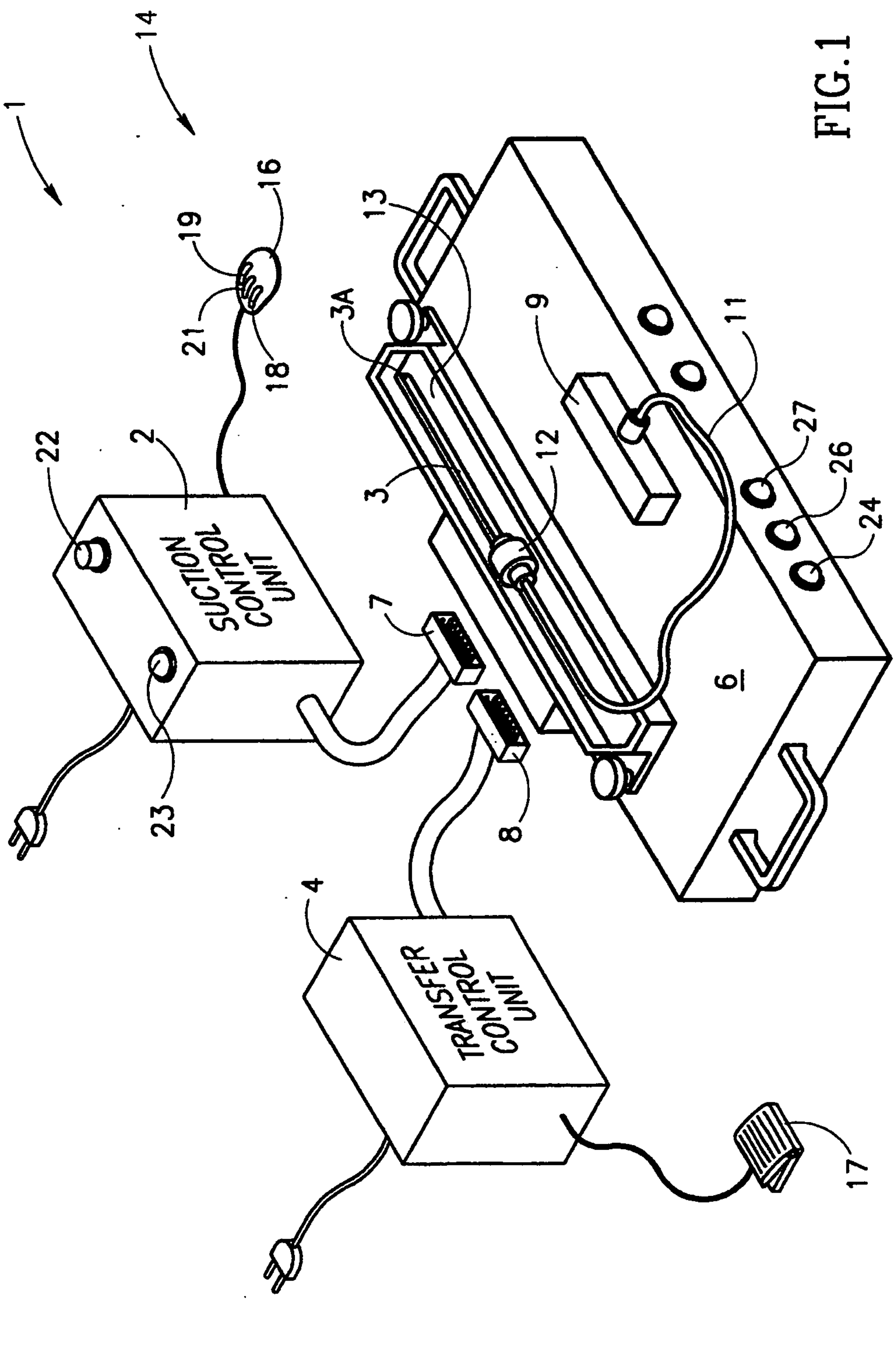

SUCTION CONTROL UNIT
TRANSFER CONTROL UNIT
1
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FIG.1

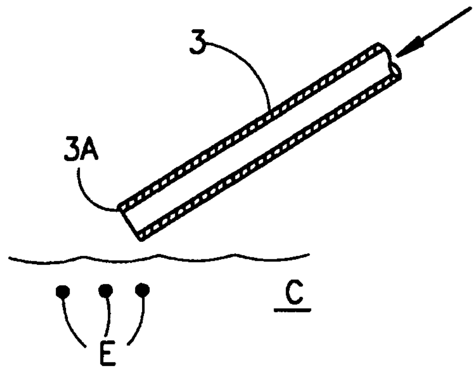

FIG.2A

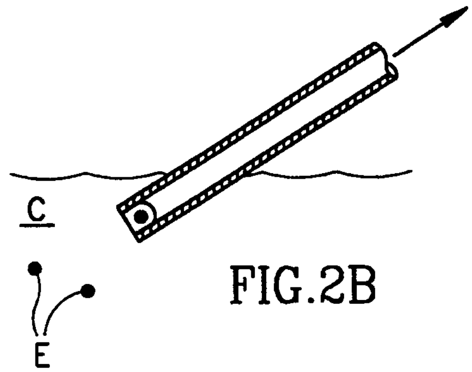

FIG.2B

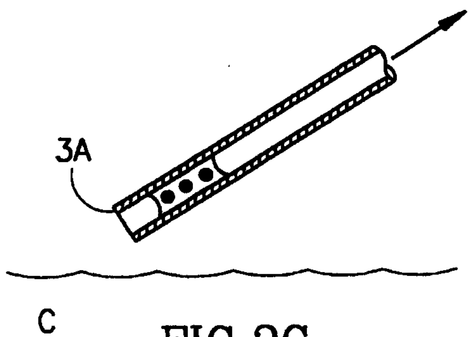

FIG.2C

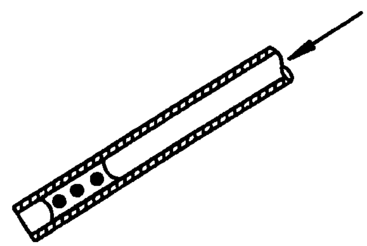

FIG.2D

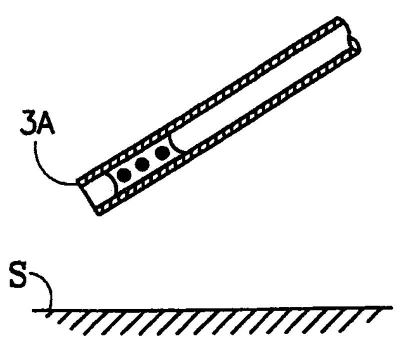

FIG.2E

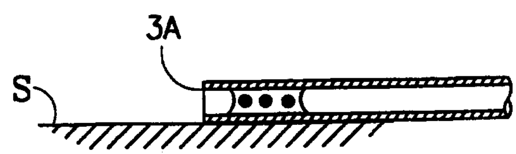

FIG.2F

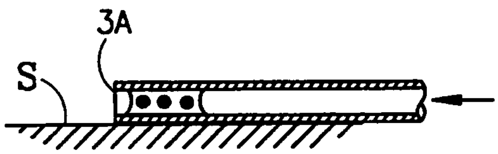

FIG.2G

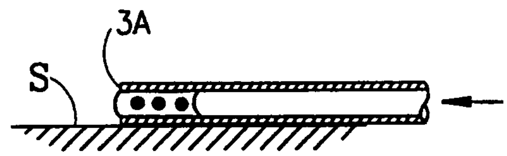

FIG.2H

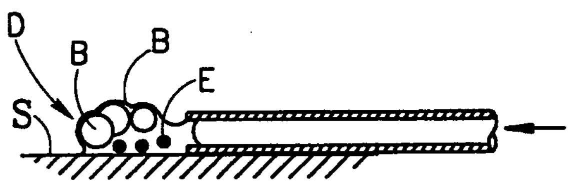

FIG.2J

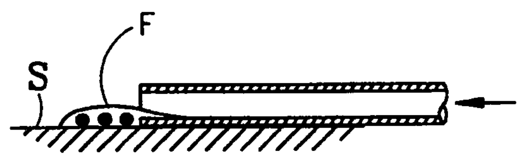

FIG.2K

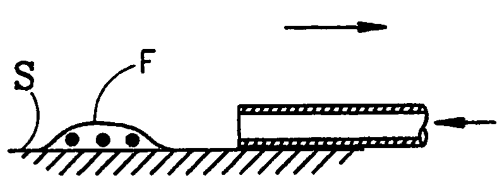

FIG.2L

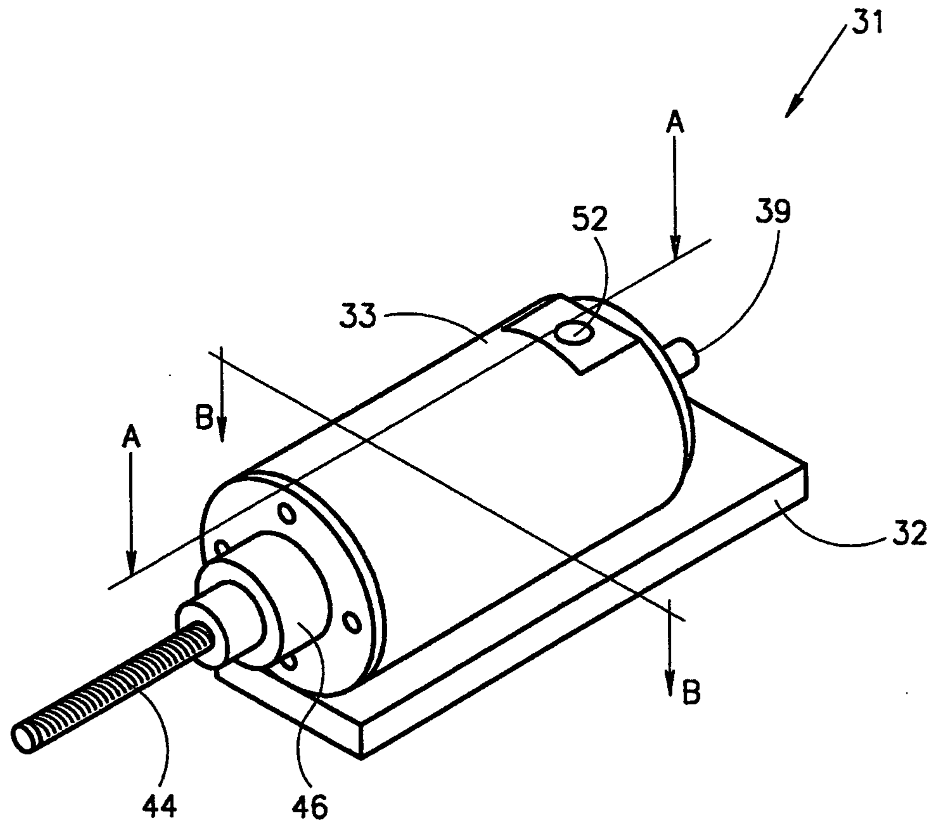

FIG.3

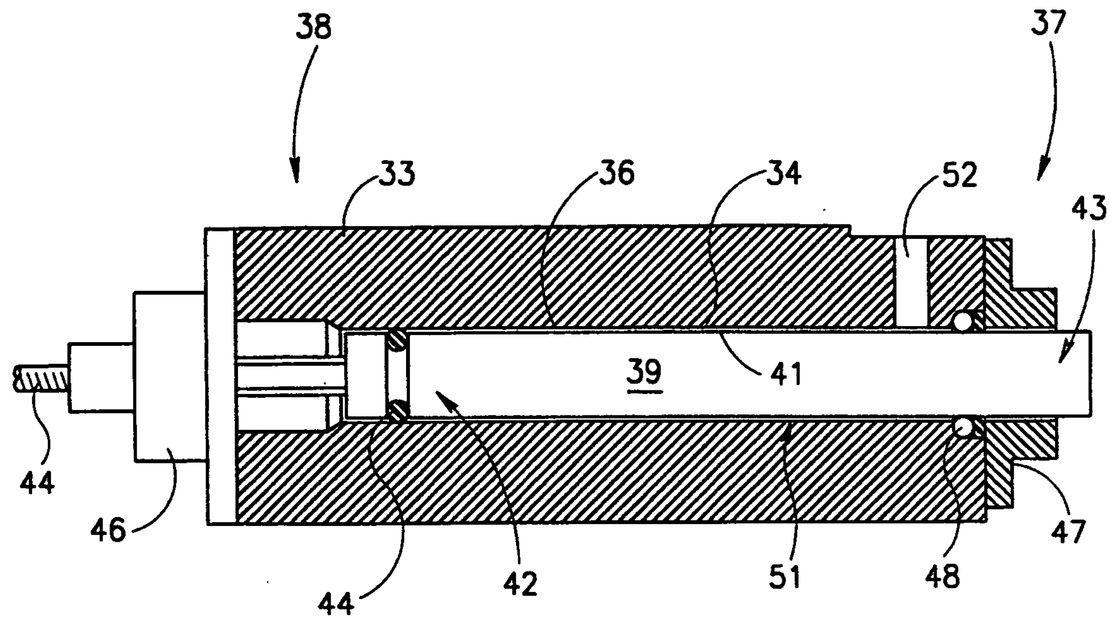

FIG.4

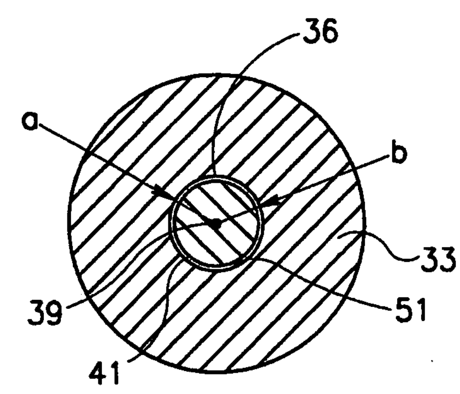

FIG.5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 98/00498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B17/435 A61D19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B B01L A61D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 982 899 A (KELM) 28 September 1976 see the whole document	1,7,10
A	DE 44 19 726 A (KWAHAK INTERNATIONAL CO., LTD.) 8 December 1994 see abstract; figures	1
A	DE 89 09 141 U (ZECH) 30 August 1990 see claims; figures	1,7
A	US 4 988 481 A (JARVIMAKI ET AL.) 29 January 1991 see abstract; figures	10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
13 January 1999	19/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giménez Burgos, R

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 98/00498

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